

REMARKS

Claims 25 and 31-35 are pending and under examination.

The claims

The claims are drawn to a method for the treatment of insulin dependent (type I) diabetes. The method includes administering to a prediabetic mammal, or a mammal having partial β cell destruction, a soluble fibronectin polypeptide comprising an EILDV motif.

Rejections under 35 U.S.C. §112, first paragraph

Claims 25 and 31-35 are rejected as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner states that:

One cannot extrapolate the teaching of the specification to the enablement of the claims because the data from the [anti-VLA-4] antibody and VCAM construct cannot be extrapolated to the enablement of the claimed method using the claimed soluble fibronectin polypeptide.

Although it is known that VLA-4 binds both fibronectin and VCAM, it is clear that the claimed soluble fibronectin polypeptide is not an inhibitor of VLA-4 dependent binding of precursor B-cells to bone marrow-derived fibroblasts [based on Ryan] or an inhibitor of VLA-4 dependent binding of T cells to type B synovial lining cells of rheumatoid arthritis patients [based on Dinter-Janssen]. Given the above, no nexus has been established between the VLA-4 inhibitory activity of the anti-VLA4 antibody/VCAM-1 construct and the claimed soluble fibronectin polypeptide.

This rejection is respectfully traversed. The fact that a soluble fibronectin polypeptide did not work as an inhibitor of VLA-4 in two specific, non-diabetes related, in vitro systems does not mean that the claims are not enabled. At the time the present application was filed, fibronectin polypeptides were known inhibitors of the VLA-4 activity. Once Applicants have established the correlation between inhibition of VLA-4 activity and the treatment of diabetes (as shown by the working Examples which disclose the use of anti-VLA-4 antibodies to treat diabetes) similar results are expected using fibronectin polypeptides.

In support of the rejection, the Examiner has cited two references where an EILDV-containing (e.g., a CS1-containing) fibronectin peptide fails to inhibit a VLA-4 activity. However, the Examiner has ignored the numerous references showing that a CS1 containing fibronectin peptide works to inhibit a VLA-4 mediated mechanism. For example, the following references show that an EILDV-containing fibronectin polypeptide inhibits a VLA-4 mediated mechanism, in a similar manner as an anti-VLA-4 antibody:

- Elices, M. et al. (1994) *J. Clin. Invest.* 93:405: This reference shows that adhesion of T lymphoblastoid cells to the synovial endothelium of rheumatoid arthritis patients was abrogated using either an anti-VLA4 antibody or a CS1-containing peptide (which contains the EILDV motif).
- Dinther-Janssen et al. (1993) *Ann Rheum Dis.* 52(9):672-6: In this reference authored by the same group as the reference cited by the Examiner, it is shown that in the presence of the CS1 peptide, 54% inhibition of binding of lymphocytes to inflamed synovium was observed while a comparable 68% inhibition was obtained with antibody to VLA-4.
- Molossi, S. et al. (1995) *J. Clin. Invest.* 95(6): 2601-2610: this reference shows that synthetic CS1 tetrapeptides, which block VLA-4 binding to fibronectin, reduce accelerated coronary arteriopathy in cardiac allograft animal models.
- Korom et al. (1998) *Transplantation* 65:854-859: this reference shows that an alternatively spliced CS1 variant of fibronectin that blocked VLA-4 binding effectively inhibited the development of chronic rejection in cardiac allograft recipients, and depressed the expression of key T cell- and macrophage-associated cytokines/chemoattractants.

Given the numerous examples in the art, such as the ones listed above, where fibronectin peptides work to inhibit VLA-4 activity, the fact that CS1-containing fibronectin polypeptides did not work in two specific references unrelated to diabetes cited by the Examiner does not mean that the claims are not enabled. Given the fact that anti-VLA4 antibodies and fibronectin peptides were known to have similar effects in various systems, it was reasonably predictable at the time of filing that fibronectin peptides would work similarly to anti-VLA4 antibodies to treat diabetes, as disclosed in the specification. Indeed, the fact that fibronectin polypeptides may not work in some systems other than diabetes is unrelated to the question of whether one of ordinary skill in the art would know how to make and use the recited fibronectin polypeptides that do work in the treatment of diabetes without undue experimentation. Taken together, the references discussed above, in combination with the examples and detailed guidance provided in the specification, support enablement.

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Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date:

9 January 2004

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